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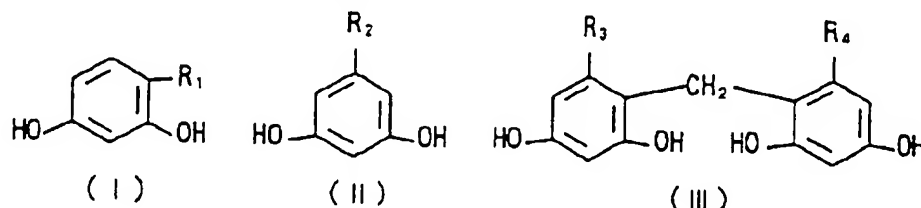
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[Claims]

[Claim 1] A cosmetic containing at least 1 type selected from the group of tyrosinase activity inhibitors represented by the formula

[Formula 1]



(In the formula, R₁, R₃ and R₄ are hydrogen atoms or alkyl bases or alkenyl bases of carbon number 1~9 and R₂ is an alkyl base or alkenyl base of carbon number 2~9.).

[Detailed Explanation of the Invention]

[0001]

[Industrial Field of Utilization] This invention pertains to cosmetics, in particular, it pertains to cosmetics having skin beautifying effects.

[0002]

[Prior Art] Melanin pigments, which are the origin of skin darkening, generate melanogenesis granules in melanin cells (melanocytes) between the epidermis and dermis and the generated melanin is dispersed to the neighboring cells. The biochemical reaction in these melanocytes, when present, is maintained as follows.

[0003] Tyrosine, which is an essential amino acid, goes from dopa to dopaquinone by the use of tyrosinase; the extent this changes red pigments and colorless pigments to very dark melanin by the oxidative or non-oxidative oxidation production is the extent of the generation of melanin pigments. Thus, the control of the synthesis of tyrosinase in order to control the production of tyrosinase which is the first step of the reaction or the control of the generation of melanin by the reduction of quinone of the intermediate step are considered possible.

[0004] Thus, when substances which control or inhibit tyrosinase synthesis or the production of tyrosinase are blended with cosmetics, beautifying effects can be maintained.

[0005] Further, as control devices, there is the proposal of the use of ones like substances which combine with copper which is the activity center of tyrosinase (for example, thiourea, cysteine and kojic acid), substances bringing about competitive substrates with tyrosine which is a substrate of tyrosine (for example, N-acetyl tyrosine, γ -pyrone and [untranslatable: hinoki]thiol), substances which extend the induction period of the reactions of tyrosinase and substrates (for example, Tween 20), substances which selectively combine with O-dihydroxy bases such as dopa (for example, molybdenum), substances that combine with O-quinone types (for example, aniline), and reducing agents for O-quinone types (or example, ascorbic acid, hydroquinone and their derivatives). Although there are cosmetics obtained by combining these melanogenesis inhibiting properties, they are not cosmetics that

can satisfy the problems produced by toxicity to humans, instability and functional group influences.

[0006] Currently, ones like hydroquinone types and resorcinol types which have long chain alkyl bases of 4 units are known as tyrosinase activity inhibitors, and tyrosinase activity inhibiting forms of hydroquinones of description in ones like the Publication of Japanese Laid Open Patents No. S61-21007, S61-21008, S61-21009, S61-21010, S61-21011 and S61-21012 are non-antagonistic agents; however, toxicity to living bodies is a concern when seen from the viewpoint of being continuously maintained within living bodies. Further, tyrosinase activity inhibitors of resorcinol types of description in the Publication of Japanese Laid-Open Patent No. H3-28462 are long alkyl chains of 4 units which hinders the solubility in water and the desired use in ordinary cosmetics is not possible. Also, arbutin, which has been used previously, is toxic. And, [untranslatable: toranekisamu] acid of description in the Publication of Japanese Laid-Open Patent No. H4-169515 has problems such as the tyrosinase activity inhibiting effect being low.

[0007]

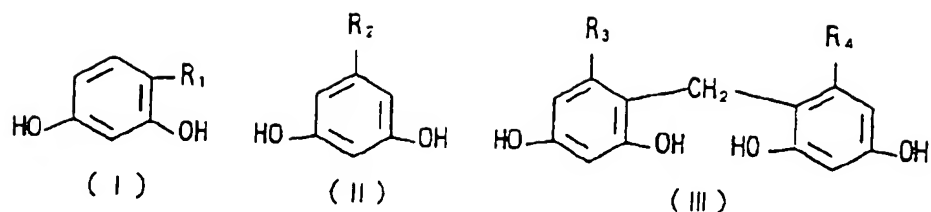
[Problems to be Solved by the Invention] This invention offers a cosmetic having low toxicity for humans and skin beautifying effects as the objective by solving the above-mentioned previous problems.

[0008]

[Means for Solving the Problems] For this invention, the formula

[0009]

[Formula 2]



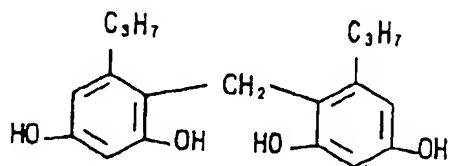
[0010] offers a cosmetic containing at least 1 type selected from the group of tyrosinase activity inhibitors represented by [the formula] (in the formula, R₁, R₃ and R₄ are hydrogen atoms or alkyl groups or alkenyl groups of 1~9 carbon atoms and R₂ is an alkyl group or alkenyl group of 2~9 carbon atoms) and the above-mentioned objective is realized by this.

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[0011] Desirably, cosmetics of this invention are blended with at least 1 type of tyrosinase activity inhibitor which is selected from the group comprised from Formulas (I) and (III). Also, desirably, cosmetics of this invention, [are blended with] at least 1 type of tyrosinase activity inhibitors which are selected from the group comprised from Formula (III), and the formula

[0012]

[Formula 3]



[0013] represents tyrosinase activity inhibitors that are

represented which are blended.

[0014] Tyrosinase activity inhibitors that are represented by the above-mentioned (I), (II) and (III) are blended by methods that are commonly known to ones skilled in the art. For example, synthesis by the various following methods is possible.

[0015] (I) Manufacturing Method

First, 2, 4-dihydroxy alkyl phenone was obtained by reacting alkyl carboxylic acid and resorcinol. Then, 4-alkyl resorcinol was obtained by reducing this using zinc amalgam which was obtained from zinc and mercury (II) salt.

[0016] (II) Manufacturing Method

First, 1,3-diethoxy alkyl phenone was obtained by reacting 1,3-dimethoxy-5-benzoyl chromide and alkyl magnesium bromide. Then, this was reduced using zinc amalgam that was obtained from zinc and mercury (II) chloride. Then, the reaction proceeded by mixing [this] with 10 to 15 cc concentrated hydrochloric acid for about 1 hour. After the reaction was completed and after cooling, 5-alkyl resorcinol was obtained by performing refining by conventional methods.

[0017] (III) Manufacturing Method

First, 5,5'-dialkyl-1,1',3,3'-tetramethoxy diphenyl methane was obtained by reacting 1,3-dimethoxy-5-alkyl benzene, phenoxy acetyl chloride and aluminum chloride. 5,5'-dialkyl-1,1',3,3'-tetrahydroxy diphenyl methane was obtained by refining this by conventional methods.

[0018] This invention can be applied to a wide field in various

cosmetics (for example, various cosmetic bases such as creams, milky lotions, face lotions, packs and facial cleansers, various makeup materials like foundations, rouge, blush and lipsticks and other cosmetics such as soaps, shampoos, rinses, toilet waters and au de colognes) by mixing through selection of at least 1 of the tyrosinase activity inhibitors that is represented by Formulas (I), (II) and (III) by dissolving or dispersing in ones like the bases which are often used in cosmetics (for example, oils such as olive oil and mink oil, lanolin and [untranslatable: tankakasuiso; probably a typographical error for: hydrocarbon] types such as waxes like that of bees, vaseline and squalane, ester types such as isopropyl palmate, high grade alcohols such as cetyl alcohol and lauryl alcohol, high grade fatty acids such as stearic acid and palmitic acid, and sterol types such as cholesterol) and alcohol types (for example, ethanol, isopropyl alcohol and propylene glycol). In these cases, combined use with various cosmetic additives (for example, various surfactants, solvents, pigments, fragrances, preservatives, antioxidants, humectants, vitamins, plant and animal extracts and other additives) is possible. Also, various forms such as solutions, emulsions, soft ointments, oils, waxes, gels, sols, powders and sprays can be utilized for the aforementioned various cosmetics.

[0019] The blended amount into the various cosmetics of tyrosinase activity inhibitors can be adequately selected and varied by the application function. In principle, the effective weight being present is fine. Generally, (for the total weight)

0.001-20 weight% is fine, with 0.01-5 weight% being desirable, when blended into cosmetic compositions.

[0020] Tyrosinase activity inhibitors which are represented by Formulas (I), (II) and (III) have low toxicity and irritation for the skin, have high stability for light and heat, have high stability, also, for various cosmetic base [materials] and additives, and can be utilized with such things as these various cosmetic base materials and additives.

[0021]

[Actual Examples] This invention is explained in further detail by the following actual examples, but this invention is not limited to these.

[0022]

[Actual Example 1]

4-ethyl resorcinol synthesis

151 g of zinc chloride was dissolved in 162 g of butyric acid. Next, 110 g of resorcinol was added and reacted for 20 minutes at 150°C. After the reaction, 250 ml of concentrated hydrochloric acid and 250 ml of water were added; after cooling, 100 g of the compound 2, 4-dihydroxy ethyl phenone was obtained by the usual refining methods. Next, 300 cc of water, 300 cc of concentrated hydrochloric acid and 100 g of 2,4-dihydroxy ethyl phenone were added to zinc amalgam, which was obtained from 400 g of zinc and 20 g of mercury (II) chloride, and reduced. Then, 10 to 15 cc of concentrated hydrochloric acid were mixed in for about 1 hour. After cooling after the reaction was completed, the reaction

solution was saturated by sodium chloride and 88 g of 4-ethyl resorcinol was obtained by extraction with ether.

[0023]

[Actual Example 2]

5-methyl resorcinol synthesis

1,3-dimethoxy methyl phenone was obtained at a 45% yield by adding 35 g of methyl magnesium bromide to 100 g of 1,3-dimethoxy-5-benzoyl chloride. Next, 300 cc of water, 300 cc of concentrated hydrochloric acid and 100 g of 1,3-dimethoxy methyl phenone were added to zinc amalgam, which was obtained from 400 g of zinc and 20 g of mercury (II) chloride, and reduced. Then, 10 to 15 cc

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concentrated hydrochloric acid was mixed for about 1 hour. After cooling after the reaction was completed, the reaction was saturated with sodium chloride and 40 g of 1,3-dimethoxy-5-methyl benzene was obtained by extraction with ether. Hydrogen iodide was added to the obtained 1,3-dimethoxy-5-methyl benzene and [this] was stirred for 3 hours at 115-125°C under nitrogen displacement; after cooling, 30 g of 5-methyl resorcinol was obtained by extraction with methylene chloride.

[0024]

[Actual Example 3]

5,5'-dipropyl-1,1',3,3'-tetrahydroxy diphenyl methane synthesis

11 g of 1,3-dimethoxy-5-propyl benzene, 11 g of phenoxy acetyl chloride and 9 g of aluminum chloride were added to 70 ml of benzene and stirred for 1.5 hours at 5°C. After hydrolysis with

hydrochloric acid in an ice bath, 0.3 g of 5,5'-dipropyl-1,1',3,3'-tetramethoxy diphenyl methane was obtained by extraction with ether. Hydrogen iodide was added to the obtained 5,5'-dipropyl-1,1',3,3'-tetramethoxy diphenyl methane and [this] was stirred for 3 hours at 115-125°C; after cooling, 0.3 g of 5,5'-dipropyl-1,1',3,3'-tetrahydroxy diphenyl methane was obtained by extraction with methylene chloride.

[0025]

[Actual Example 4]

Tyrosinase Activity Inhibition Rate Measurements of Tyrosinase Activity Inhibitors Obtained in Actual Example 1-3

Measurements were performed by the following methods.

(1) Reaction Series Reagents

Those used as the reaction series reagents were as follows.

Substrate: 2 mM L-dopa ([untranslatable: Wakojunyaku;
probably a trade name])

Buffer Solution: 0.1 M potassium phosphate (pH6.8))
solution

Inhibitors: compound shown in Formula (I), 4-ethyl
resorcinol; compound shown in Formula (II),
5-methyl resorcinol; compound shown in Formula
(III), 5,5'-dipropyl-1,1'-3,3'-tetrahydroxy
diphenyl methane; each 1% solutions

Enzyme: Tyrosinase (Sigma, Co..) 0.5 mg/ml

[0026] (2) Tyrosinase Activity Inhibition Rate Measurement

Reaction Solution Preparation

No. 1, No. 2 and No.3 sample solutions, which were blended in the proportions which are shown in the following Table 1, were respectively prepared for spectrophotometer cells (1 ml) when measuring tyrosinase activity.

[Table 1]

| <u>Sample Solution Compositions (ml)</u> | | | |
|--|-------|-------|-------|
| | No. 1 | No. 2 | No. 3 |
| Buffer Solution | 0.50 | 0.50 | 0.50 |
| Substrate | - | 0.20 | 0.20 |
| Inhibitor | - | - | 0.10 |
| Deionized Water | 0.48 | 0.28 | 0.18 |

Measurement

Enzyme solution was added to the cells (0.20 ml) and the absorbance at 471 nm was measured over the passage of time from after 3 minutes from the addition time by spectrophotometer. The inhibition rate was calculated by the following formula for the absorbance of No. 3 (Ab.3) and the absorbance of No. 1 (Ab. 1) at the time representing the maximum value of the absorbance of No. 2 (Ab. 2). The results are shown in the following Table 2.

$$\text{Inhibition (\%)} = \{1 - (\text{Ab.3} - \text{Ab.1} / \text{Ab.2} - \text{Ab.1})\} \times 100$$

[Table 2]

| <u>Tyrosinase Activity Inhibitor</u> | <u>Tyrosinase Activity Inhibition</u> |
|--------------------------------------|---------------------------------------|
| | <u>Rate %</u> |

| | |
|---|------|
| 4-ethyl resorcinol | 93.1 |
| 5-methyl resorcinol | 90.9 |
| 5,5-dipropyl-1,1',3,3'- tetrahydroxy diphenyl methane | 83.9 |

[0027]

[Actual Example 5]

Measurement of Melanogenesis Inhibition Function of the Tyrosinase Activity Inhibitors of Actual Examples 1~3

Tyrosinase synthesis inhibition for melanocytes and tyrosinase inhibition function were evaluated as in the following by the use of incubation pigment cells.

(1) Experimental Medium Preparation

1.25 ml of 1% solution of the tyrosinase activity inhibitors obtained in Actual examples 1, 2 or 3 were added to 45 ml of Baggle's MEM medium which did not contain [bovine] blood agar, and 2 ml of blood agar was added as the experimental medium after filtering with a 0.2 μ m filter.

[0028] (2) Test Method

4 ml of experimental medium was put into a 6 cm diameter Schale[?] and $1 \times 10^5/0.2$ ml of incubation pigment cells (B-16 melanoma) were added and incubated for 6 days in a 37°C, 5% carbonic acid gas•air mixed environment and the experimental medium was changed after 4 days. After 6 days, 0.025% trypsin and 0.01% EDTA mixed solution was added and the cells were suspended, and the

pigment cells were collected by centrifuging for 10 minute at 700 rpm, and the biosynthesized melanin amount was measured by spectrophotometer at 660 nm. The melanin biosynthesis amount from incubation without the addition of the tyrosinase activity inhibitors which were obtained in Actual Examples 1, 2 or 3 was the standard reference and the tyrosinase biosynthesis inhibition rate was determined by the following formula. The results are shown in Table 3.

melanin biosynthesis inhibition rate={1-(experiment medium cell melanogenesis amount/melanogenesis amount of standard reference)} X 100%

[Table 3]

| <u>Tyrosinase Activity Inhibitor</u> | <u>Melanogenesis Activity</u> |
|--|-------------------------------|
| | <u>Inhibition Rate%</u> |
| 4-ethyl resorcinol | 95.6 |
| 5-methyl resorcinol | 92.9 |
| | /5 |
| 5,5-dipropyl-1,1',3,3'- tetrahydroxy diphenyl methane | 90.2 |

[0029]

[Actual Example 6]

Cream

An aqueous phase was prepared by heating and blending tyrosinase activity inhibitors obtained in Actual Examples 1, 2 and 3, which were dissolved in propylene glycol, potassium hydroxide

and preservatives and antioxidants at approximately 75°C and an oil phase was prepared by heating and blending beeswax, stearyl alcohol, stearic acid, squalane, glycerin[sic] monostearate and polyoxy ethylene stearate at approximately 80°C; then, the oil phase was gradually added and suspended in the water phase. After that, [this] was cooled to approximately 35°C and fragrance was added and this was cream. The obtained cream showed adequate stability. The compound composition is shown in the following Table 4.

[Table 4]

| Composition | (Weight%) |
|---|-----------------|
| 4-ethyl resorcinol | 1.0 |
| 5-methyl resorcinol | 1.0 |
| 5,5-dipropyl-1,1',3,3'-tetra- hydroxy diphenyl methane | 1.0 |
| beeswax | 2.0 |
| stearyl alcohol | 5.0 |
| stearic acid | 8.0 |
| squalane | 10.0 |
| glyceryl monostearate | 3.0 |
| polyoxy ethylene stearate | 1.0 |
| propylene glycol | 5.0 |
| potassium hydroxide | 3.0 |
| fragrance | adequate amount |
| preservatives•antioxidants | adequate amount |
| pure water | remainder |

[0030]

[Actual Example 7]

Suspension

An aqueous phase was prepared by heating and blending propylene glycol, carboxyvinyl polymer, potassium hydroxide and preservatives•antioxidants with pure water at approximately 75°C and an oil phase was prepared by heating and blending beeswax, squalane, vaseline, sorbitan sesquioleate and polyoxy ethylene oleyl ether at approximately 80°C; then, the oil phase was gradually added to the water phase and suspended. After that, [this] was cooled to approximately 35°C, and fragrance and the tyrosinase activity inhibitors, which were obtained in Actual Examples 1, 2 and 3, were dissolved in ethanol and added as a suspension. The obtained suspension showed adequate stability. The compound composition is shown in the following Table 5.

[Table 5]

| Composition | (Weight%) |
|---|-----------|
| 4-ethyl resorcinol | 1.0 |
| 5-methyl resorcinol | 1.0 |
| 5,5-dipropyl-1,1',3,3'-tetrahydroxy diphenyl methane | 1.0 |
| squalane | 8.0 |
| vaseline | 2.0 |
| beeswax | 0.5 |
| sorbitan sesquioleate | 0.8 |

| | |
|------------------------------|-----------------|
| polyoxy ethylene oleyl ether | 1.2 |
| carboxyvinyl polymer | 0.2 |
| propylene glycol | 5.0 |
| potassium hydroxide | 0.1 |
| ethanol | 7.0 |
| fragrance | adequate amount |
| preservatives•antioxidants | adequate amount |
| pure water | remainder |

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[0031]

[Actual Example 8]

Toilet Water

Compounds were prepared of humectants like glyceryl added to pure water, and, uniquely for this, ones like preservatives, fragrances, surfactants and tyrosinase activity inhibitors obtained in Actual Examples 1, 2 and 3 were dissolved in alcohol and mixed and were soluble and [this] was a toilet water. The obtained toilet water showed adequate stability. The compound composition is shown in the following Table 6.

[Table 6]

| Composition | (Weight%) |
|------------------------------------|-----------|
| 4-ethyl resorcinol | 1.0 |
| 5-methyl resorcinol | 1.0 |
| 5,5-dipropyl-1,1',3,3-tetrahydroxy | 1.0 |
| diphenyl methane | |

| | |
|---|-----------------|
| glycerin | 5.0 |
| polyoxy ethylene oleyl ether | 1.5 |
| propylene glycol | 4.0 |
| oleyl alcohol | 0.1 |
| polyoxy ethylene sorbitan | |
| monolaurate (20.E.O.) | 1.5 |
| poly oxyethylene lauryl ether (20.E.O.) | 0.5 |
| ethanol | 10.0 |
| fragrance | 0.1 |
| preservatives | adequate amount |
| pure water | remainder |

[0032]

[Actual Example 9]

Pack

Ones like humectants such as glycerin were added to pure water, and, expanded by the use of coating agents like poly(vinyl alcohol)-vinyl acetate emulsions, powders such as kaolin and titanium oxide were added in response to need; uniquely in this, ethanol was added with ones like preservatives, fragrances and the tyrosinase activity inhibitors obtained in Actual Examples 1, 2 and 3 were dissolved, and this was kneaded until a paste was formed. This pack showed adequate stability. The compound composition is shown in the following Table 7.

[Table 7]

| Composition | (Weight%) |
|---|-----------------|
| 4-ethyl resorcinol | 1.0 |
| 5-methyl resorcinol | 1.0 |
| 5,5-dipropyl-1,1',3,3'-tetrahydroxy diphenyl methane | 1.0 |
| vinyl acetate emulsion | 15.0 |
| polyvinyl alcohol | 10.0 |
| olive oil | 3.0 |
| glycerin | 5.0 |
| titanium oxide | 8.0 |
| kaolin | 7.0 |
| ethanol | 5.0 |
| fragrance | 0.1 |
| preservatives•antioxidants | adequate amount |
| pure water | remainder |

[0033]

[Actual Example 10]

Hair Tonic

Humectants such as glycerin were added to pure water and dissolved as the aqueous phase and, uniquely in this, the aqueous phase was added little by little to ethanol with ones like preservatives, fragrances and the tyrosinase activity inhibitors obtained in Actual Examples 1, 2 and 3 dissolved; after being uniformly blended, [this] was cooled and filtered and was hair tonic. This hair tonic showed adequate stability. The compound

composition is shown in the following Table 8.

[Table 8]

| Composition | (Weight%) |
|---|-----------------|
| | /7 |
| 4-ethyl resorcinol | 1.0 |
| 5-methyl resorcinol | 1.0 |
| 5,5-dipropyl-1,1',3,3'-tetrahydroxy diphenyl methane | 1.0 |
| ethanol (95%) | 75.0 |
| glycerin | 5.0 |
| fragrance | 0.1 |
| preservatives | adequate amount |
| pure water | remainder |

[0034]

[Actual Example 11]

Milky Liquid Foundation

An aqueous phase was prepared by blending tyrosinase activity inhibitors obtained in Actual Examples 1, 2 and 3, that were dissolved in propylene glycol, with carboxymethyl cellulose sodium, bentonate, triethanol amine, methyl peroxybenzoate and preservatives in pure water at approximately 75°C and an oil phase was prepared by heating and blending stearic acid, propylene glycol monostearate, cetostearyl alcohol, liquid form lanolin, fluid paraffin, isopropyl myristate and propyl peroxybenzoate at

approximately 80°C; then, the oil phase was suspended by being gradually added to the aqueous phase. After that, fragrance was added and [this] was cooled to approximately 35°C and milky lotion form foundation was obtained. This foundation showed adequate stability. The compound composition is shown in the following Table 9.

[Table 9]

| Composition | (Weight%) |
|---|-----------------|
| 4-ethyl resorcinol | 1.0 |
| 5-methyl resorcinol | 1.0 |
| 5,5-dipropyl-1,1',3,3'-tetrahydroxy diphenyl methane | 1.0 |
| stearic acid | 2.4 |
| propylene glycol monostearate | 2.0 |
| cetostearyl alcohol | 0.2 |
| liquid lanolin | 2.0 |
| fluid paraffin | 3.0 |
| isopropyl myristate | 8.5 |
| peroxybenzoate | adequate amount |
| pure water | remainder |
| carboxymethyl cellulose sodium | 0.2 |
| bentonate | 0.5 |
| propylene glycol | 4.0 |
| triethanol amine | 1.1 |
| methylperoxy benzoate | adequate amount |

| | |
|-----------------|-----------------|
| titanium oxide | 8.0 |
| talc | 4.0 |
| facial colorant | adequate amount |
| fragrance | adequate amount |
| preservatives | adequate amount |

[0035]

[Effects of the Invention] Cosmetics with low toxicity to humans and beautifying effects are offered that can be suitably utilized for skin cosmetics, especially, in various product forms such as various cosmetic creams, milky lotions, toilet waters, packs, lipsticks, base makeup, foundations and suncare [lotions].

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[Procedural Revision]

[Presentation Date] November 17, 1992

[Procedural Revision 1]

[Revision Subject Name] Specifications

[Revision Subject Item] 0006

[Revision Method] Change

[Revision Contents]

[0006] Currently, ones like hydroquinone types and resorcinol types which have long chain alkyl bases of 4 units are known as tyrosinase activity inhibitors, and tyrosinase activity inhibiting forms of hydroquinones of description in ones like the Publication of Japanese Laid Open Patents No. S61-21007, S61-21008, S61-21009, S61-21010, S61-21011 and S61-21012 are non-antagonistic agents;

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